# STUDIES
# IN BRONCHIAL ASTHMA

*A Comparative Examination*
*between Endogenous and Exogenous Bronchial Asthma*
*in Adult Patients.*

AV

ERIK FAGERBERG

UPPSALA 1958

# STUDIES
# IN BRONCHIAL ASTHMA

*A Comparative Examination*
*between Endogenous and Exogenous Bronchial Asthma*
*in Adult Patients.*

AKADEMISK AVHANDLING

SOM MED TILLSTÅND AV MEDICINSKA FAKULTETEN
VID UPPSALA UNIVERSITET FÖR ERNÅENDE AV MEDICINE DOKTORSGRAD
OFFENTLIGEN FÖRSVARAS Å PATOLOGISKA INSTITUTIONEN
LÖRDAGEN DEN 27 SEPTEMBER 1958 KL. 10 F. M.

AV

ERIK FAGERBERG
Med. lic., Norrl.

UPPSALA 1958
APPELBERGS BOKTRYCKERI AB

# STUDIES
# IN BRONCHIAL ASTHMA

*A Comparative Examination*
*between Endogenous and Exogenous Bronchial Asthma*
*in Adult Patients.*

BY

ERIK FAGERBERG

R. UNIV.
BIBLIOTHEEK
LEIDEN

UPPSALA 1958
APPELBERGS BOKTRYCKERI AB

Uppsala 1958
Appelbergs Boktryckeri AB

The present publication is based on the following papers:

I. Fagerberg, E.: Examination of Patients with Bronchial Asthma. Occurrence of Asthma without and with Specific Allergy as the Cause of the Disease. Acta Allergol. XI, 293, 1957.

II. Fagerberg, E.: A Comparative Examination between Patients with Endogenous and Exogenous Bronchial Asthma respectively with Regard to Age when taken ill. Acta Allergol. XI, 327, 1957.

III. Fagerberg, E.: A Comparative Examination between Patients with Endogenous and Exogenous Bronchial Asthma with Respect to Blood Sedimentation Rate. Acta Allergol. XII, 1, 1958.

IV. Fagerberg, E.: A Comparative Examination between Patients with Endogenous and Exogenous Bronchial Asthma with Respect to the Part played by Infection for the first Onset of the Complaint. Acta Allergol. XII, 17, 1958.

References to these papers will be made by using the Roman numerals, as above.

## INTRODUCTION

Bronchial asthma is now considered to be an allergic complaint. There are also many cases where it is possible to show through prehistories, skin tests, and provocation tests that the releasing factor for asthmatic distress is one or more allergens, and where it is possible to improve or cure the patients for instance by hyposensitization or elimination of the allergens (extrinsic, allergic, sensitive, non-infective etc. types of asthma). On the other hand we also know that there are a number of cases where it is not possible to find evidence for any such specific allergy with the

present diagnostic aids at our disposal, and where one has no possibility of relieving the distress with specific hyposensitization or elimination of the allergens (intrinsic, non-allergic, non-sensitive, infective, psychogenic, unspecific reflex etc. types of asthma). Besides there are of course cases of mixed allergic and non-allergic asthma. The number of patients belonging to the first-mentioned group varies according to different authors' investigations from about 20 % to about 75 %. *Bruun*, however, is of the opinion that in most cases (probably all) asthma is an allergic condition and that in most cases an adequate exogenous allergen can be demonstrated as the etiological cause. The reason why it is impossible to point to specific allergens as releasing causes of asthma in the case of each individual patient, and why there are such wide differences in different authors' investigations concerning the frequency of extrinsic and intrinsic asthma may be:

1. Shortcomings of investigations and allergen extracts.
2. The fact stressed by some authors (*Abderhalden, Rackemann, Tuft, Davison, Gumpert*) that bronchial asthma which starts before 30 years of age is as a rule allergic, and that which starts after 40 years of age non-allergic. If these observations are correct, the age distribution of the material investigated must necessarily influence the frequency of extrinsic and intrinsic asthma respectively. If the material consists of mainly young people, who contracted asthma at an early age, the incidence of extrinsic asthma should be greater than if the material mainly consists of adults with whom the asthma began at a later age.

The present work comprises 400 hospitalized and 348 outpatients, all of them more than 18 years old. The material has been divided into two main groups. Patients with whom it has been possible to show that exterior allergens in the form of inhalants, food-stuffs, drugs, etc. have been important factors in the development of the asthma, have been assembled in one group, to be referred to in the following as exogenous asthma. Patients with whom it has not been possible to show the influence of any such exterior allergens have been assembled in another group to be referred to in the following as endogenous asthma. This grouping is necessarily a rough one but has been adopted for practical

reasons. The exogenous group consists of 17.8 % and the endogenous group of 82.2 %. Endogenous asthma therefore has a dominating role in this material.

As far as the author has been able to discover no extensive comparative investigation concerning exogenous and endogenous asthma, and referring only to adult patients, has been published. The purpose of the present work has been to make some comparative examinations of these types. As a basis for the examination, prehistories and clinical data from the above 748 patients (288 men and 460 women) have been submitted. In order to complete the investigation the author has also sent out questionnaires. In the majority of the cases the patients were resident in Stockholm.

# PERSONAL INVESTIGATIONS

## CHAPTER I

As has been mentioned above, the present material comprises 17.8 % cases of exogenous and 82.2 % of endogenous asthma. The classification of the patients into these two groups of asthma has been made with the help of prehistories, physical examination, laboratory tests, x-ray, intracutaneous skin tests and provocation tests. The investigations gave the following results.

Positive skin tests occurred mainly in the younger age groups. The number of patients with positive skin reactions decreased with increasing age. Thus positive reactions were found in 85.5 % with the patients under 25 years of age at the time of the tests, in 59.6 % with patients between 25–34, in 39.2 % with patients between 35–44, in 30 % between 45–54, in 28.6 % between 55–64 and in 14.1 % with patients more than 65 years of age.

Positive skin tests by themselves were not sufficient to decide whether the positive skin reactions were only an expression of a skin allergy, or had a clinical significance. Out of the 748 patients, 280 (37.5 %) had a total of 1107 positive skin reactions, 78.5 % of which were caused by inhalants and 21.5 % by food-stuff allergens. By help of the prehistories and provocation tests, however, only 195 of the skin reactions were shown to have any clinical significance in 133 (17.8 %) cases.

All the provocation tests were carried out by inhalation of different antigen extracts through a nebulizer driven by compressed air, except in the suspected cases of hypersensitivity to food-stuffs, where the allergens were introduced per os. In all the 133 cases except one, inhalants provoked the asthma, in the first place dust, and secondly pollen of different kinds and animal epithelials. These results show very convincingly that one cannot use skin tests only as an indication of exogenous and endogenous asthma. The examination must be supplemented by a careful prehistory and clinical investigation including exposure and provocation tests.

The examination also yielded the following results: The whole material was composed of 38.5 % men and 61.5 % women. In

the exogenous group, however, there was a clear predominance of men, *viz.* 56.4 % men and 43.6 % women. The predominance of the women thus occurred in the endogenous group, *viz.* 34.6 % men and 65.4 % women.

## CHAPTER II

Concerning ages of onset of asthma there are a great many publications.

A widespread idea is that asthmatic seizure in a great percentage occurs in childhood and in 70 % to 80 % before 40 years of age. In these investigations, as a rule, no information is given as to the age composition of the patient material on the occasion of examination. Some authors, however, have made their investigations with that thought in mind. When it is clearly stated that adult patients in different age groups are concerned, they have found that the onset can occur at any age and without special predominance in childhood. These authors have, however, not said anything about the composition of the material investigated in exogenous and endogenous asthma. *Rackemann* who has divided his material into cases of extrinsic and intrinsic asthma found that the onset occurred earlier in the former group than in the latter.

The present study confirms the view that the onset of asthma can occur at different ages and without special predominance in childhood, as far as *endogenous* asthma is concerned. Thus only 13.3 % of the patients with endogenous asthma were taken ill before 18 years of age, 28.4 % between 18–34, 24 % between 35–44 and 34.3 % after 45 years of age. With *exogenous* asthma, on the other hand, the present investigation confirms the view that the onset of asthma appears to occur in a great percentage in childhood and youth. Among the patients with exogenous asthma, 49.5 % were taken ill before 18 years of age, 34.5 % between 18–34, 13.6 % between 35–44, and only 2.4 % after 45 years of age. The results of the present investigation show great conformity to those of *Rackemann.*

We can also see that there is a definite difference concerning the age distribution of the patients in exogenous and endogenous asthma. For the endogenous cases the age of the patients for the most part was over 35, *viz.* 13.7 % under 35 and 86.3 % over 35 but for the exogenous cases 57 % were under 35 and 43 % over 35 years of age. *Schwartz* has also paid attention to this fact. He found that there was a marked difference concerning the age distribution of the patients at the time of examination between "allergic" and "non-allergic" asthma. In the "non-allergic" group the age groups from 35 years and upward were considerably larger than in the "allergic" group.

*Rackemann* has stated that exogenous asthma is due to allergy and that allergy is a disease of young people. The disease begins at an early age. Endogenous asthma on the other hand begins at a later age and is as a rule not due to allergy. The result of the present investigation also makes one feel inclined to suggest the use of age of onset as a means of deciding whether it is a case of exogenous or endogenous asthma. A patient who is taken ill after 35 to 45 years of age should be less likely to be suffering from exogenous asthma as long as his prehistory does not clearly indicate the presence of specific allergy. In a great number of those cases where the onset has occurred after 35–45 years of age it ought therefore to be possible to decide solely with the help of age of onset and prehistory whether the case is one of exogenous or endogenous asthma. At all events it should be possible in these cases to limit the i.c. tests to comprise inhalants only. Instead, the importance of a particularly thorough anamnesis must be stressed.

## CHAPTER III

Common to the literature is that investigations concerning blood sedimentation rate (BSR) in asthma are based on a limited patient material and without detailed accounts of its composition. A prevalent opinion is that BSR is normal or subnormal in uncomplicated asthma whilst an increase of the same indicates

complications, especially infections. Some authors have pointed out, however, that the differences are too insignificant to use BSR for differentiating between asthma with and without infection (*Urbach, Henriksen, Gay*).

In the present investigation the BSR was estimated according to *Westergren*'s method. The patients have been divided in different groups with regard to BSR. Patients with a normal BSR have been assembled in a first group. As a normal value for men under 35 years, BSR has been given at the most 5 mm/hour and for women under 35 years at the most 10 mm/hour. For men over 35 years the corresponding limit has been 10 mm/hour and for women over 35 years 20 mm/hour. In a second group those patients have been assembled, who had a BSR from the above-stated normal values to 15 mm/hour, in a third group those between 15–35 mm/hour and in a fourth group those more than 35 mm/hour.

The present examinations have given the following results: In the patients with endogenous asthma a normal BSR was present in 47.6 % and an increased one in 52.4 %. In the patients with exogenous asthma a normal BSR occurred in 67.2 % and an increased one in 32.8 %. It is obvious therefore that there was a greater percentage of increased BSR amongst endogenous cases than amongst exogenous cases.

In all the hospitalized patients the occurrence of respiratory tract infections and other infections or complications causing a raised BSR has been investigated. When all the patients are excluded, who had an increased BSR in all probability from other causes than respiratory tract infections, the following results were obtained: In endogenous asthma there was a respiratory tract infection in 17.4 % of the cases with a normal BSR and in 54.1 % with an increased BSR, and in cases of exogenous asthma in 2.7 % and 33.3 % respectively.

Rises of the anti-streptolysin (AS) and anti-staphylosin (ASt) titres have been considered as indices of an acute and even more so, of a chronic infection. These titres were examined in the hospitalized patients, usually the day after their entry into the hospital. As titre rises were regarded for AS rates of 200 units

or more and for ASt 1.4 units or more. High titres were found in 49.5 % of the cases with endogenous and in 62.7 % of the cases with exogenous asthma. If we take into account the fact that there is a characteristic age factor implying a lower rate of increase in the titres of old people the figures are fairly similar. In the endogenous cases with high titres 32 % had a normal BSR, 10.6 % of which had a respiratory tract infection, and 68 % a raised BSR, 32 % of which had a respiratory tract infection. In the exogenous cases with high titres 51.3 % had a normal BSR, 5.3 % of which had a respiratory tract infection, and 48.7 % a raised BSR, 16.6 % of which had a respiratory tract infection.

In this material there were, accordingly, signs of infections causing a raised BSR in many cases of endogenous as well as of exogenous asthma. The investigations have shown, however, that one cannot decide with the help of BSR whether asthma is present with or without infections in the respiratory tract, though an increased BSR makes such an infection more likely than a normal BSR.

## CHAPTER IV

In order to obtain a maximum of information concerning a complaint it is among other things of great importance

1. to obtain the most exact knowledge possible concerning the detailed circumstances in connection with the onset of the complaint,
2. to distinguish the causes of the onset from such factors that later induce or maintain the symptoms of the complaint.

Concerning asthma, there are given a number of observations regarding such causes as can be considered to provoke or maintain the distress in a person who has already become asthmatic, e. g. pollen, dust, animal epithelials, foodstuffs, drugs, infections, psychogenic and climatic factors. The question that arises is, however, why the patient ever started to react with asthmatic distresses to the above named causes.

It is a well-known fact that infections are a decisive factor in the occurrence of asthma. Many authors hold the view that they are of secondary importance, but many are of opinion that infections in the respiratory tract and lungs can be considered to be the *direct* cause of the onset of asthma. In the works of different authors the data seem to show a clear connection between infections and the onset of the asthma in a percentage of cases ranging from 30 to 100.

Partly with the support of records, partly with the aid of questionnaires, the present author has found that in a great percentage of the patients such infections must be considered to have great significance for the onset of asthma. Thus 61.9 % of the patients with endogenous asthma stated that the asthma began as a result of infections in the respiratory tract. Of the patients with exogenous asthma there was such a connection in 42.8 % of the cases. The role of infections as a main starting factor for the onset of the asthma must therefore be considered of importance. One can agree with Westergren's statement that "there can scarcely be any doubt as to the significance of the influence of infections not only in bronchitis asthmatica but also in endogenous asthma on the whole, but this is not to say that similar factors should be excluded in the cases of exogenous bronchial asthma. Even cases of this type have normally developed in association with an acute infection of the respiratory tract."

## GENERAL SUMMARY

1. The present investigation comprises 748 patients over 18 years of age with asthma. The majority of the patients were resident in Stockholm.

It has been possible to prove the existence of asthma with evident specific allergy (exogenous asthma) in only 17.8 % of the cases examined. In all cases except one the causes were inhalants.

The other cases (82.2 %) have either been completely negative to intracutaneous skin tests or, in a lesser number of cases, have had positive skin reactions, which however lack supporting data from the prehistories and provocation tests (endogenous asthma).

The investigation has shown very decisively that one cannot use skin tests only as an indication of exogenous and endogenous asthma respectively. The examination must be supplemented by a careful prehistory and clinical investigations preferably including exposure and provocation tests.

2. Thus it has been possible to treat only a minority of the cases with specific hyposensitization. With the remaining cases it has proved necessary to apply other methods of treatment. It is, however, of extreme importance that all patients with specific allergy to certain allergens are discovered and treated. In these cases we often see a good result for long time.

3. Women predominate in the total material, *viz.* 38.5 % men and 61.5 % women. In the cases of exogenous asthma there is, however, a clear predominance of men, *viz.* 56.4 % men and 43.6 % women. The predominance of women thus occurred in the endogenous group, *viz.* 34.6 % men and 65.4 % women.

4. In the cases examined, the patients with endogenous asthma have as a rule been taken ill at an adult age, *viz.* 13.3 % before 18, 28.4 % between 18–34, 24 % between 35–44, and 34.3 % after 45 years of age. A comparison with patients suffering from exogenous asthma shows that a very much larger percentage of these were taken ill in childhood and adolescence, *viz.* 49.5 % before 18, 34.5 % between 18–34, 13.6 % between 35–44, and

2.4 % after 45 years of age. The age distribution is also different. In the endogenous group the age of the patients at the time of examination is in 13.7 % under 35 and in 86.3 % over 35 years of age. In the exogenous group the corresponding figures are 57 % and 43 % respectively.

5. Often it should be possible to limit the standard skin tests as an aid to diagnosis to such patients as have contracted asthma before the age of 35–45 years. In such cases where the onset has occurred later it ought to be possible to decide only with the help of the age of onset and prehistory whether the case is one of endogenous or exogenous asthma. At all events the standard skin tests should in these cases be limited to inhalants.

6. The blood sedimentation rate (BSR) is often increased in this material, especially with endogenous asthma, *viz.* in 52.4 % of the cases with endogenous and in 32.8 % with exogenous asthma. According to this investigation the BSR is also more often increased in cases with infections in the respiratory tract than in cases without any evidence of such infections. The BSR cannot however, be used to differentiate between asthma of various types. An increased BSR, however, renders infections in the respiratory tract more likely than a normal BSR.

7. 61.9 % of the patients with endogenous asthma are of opinion that their asthma began as a result of infection in the respiratory tract. Amongst the patients with exogenous asthma, however, a great percentage have also given this reason, namely 42.8 %. One is therefore entitled to state that infections play a considerable part not only secondarily but perhaps also primarily as the main starting factor in both endogenous and exogenous asthma.

8. The observations made in the present investigation justify, I think, the opinion that it is very important to use a therapy aiming at reducing the activity of the infections concerned, partly by fighting an actual infection, partly by adopting prophylactic measures of different kinds with a view to diminishing the influence of the infections.

## ACKNOWLEDGEMENTS

I wish to express my gratitude to Professor Erik Ask-Upmark, M. D., who has supported my work in every way.

I am indebted to Helge Colldahl, M. D., who has given me kind support and much good advice.

I wish to thank Professor Alf Westergren, M. D. for all his advice and stimulating interest in my work.

I also wish to thank Hans Arnoldson, M. L. and Stig Wiholm, M. L., who have given me good advice.

Thanks are also due to my father, Georg Fagerberg, for valuable technical assistance, and to Bertil Sandahl, F. D., and Erik Frykman, F. L. for translating the Swedish text.

REFERENCES

*Abderhalden, R.*: Grundrisse der Allergie. B. Schwabe, Basel, 1950, p. 93.

*Bruun, E.*: In *van Ufford*: The Therapy of Bronchial Asthma. H. E. Stenfert Kroese NV., Leiden, 1956, p. 15.

*Davison, F. W.*: Ann. Otol., Rhin., and Laryngol., 62, 859, 1953.

*Gay, L. N.*: The Diagnosis and Treatment of Bronchial Asthma. Williams and Wilkins Co., Baltimore, 1946, p. 117.

*Gumpert, T. E.*: Acta Allergol., XI, 161, 1957.

*Henriksen, E.*: Asthma Bronchiale. Thesis. Dansk Videnskabs Forlag A/S, Copenhagen, 1951, p. 38.

*Rackemann, F. M.*: In *Cecil and Loeb*: Textbook of Medicine. W. B. Saunder, Philadelphia and London, 1951, p. 460.

——: J.A.M.A. 142, 534, 1950.

*Rackemann, F. M., Burrage, W. S.*, & *Irwin, J. W.*: Postgraduate Med. 8, 134, 1950.

*Schwartz, M.*: Acta Allergol. Suppl. II. 1952.

*Tuft, L.*: Clinical Allergy. W. B. Saunder, Philadelphia and London, 1937, p. 311.

*Urbach, E.* & *Gottlieb, Ph. M.*: Allergy. W. Heinemann, London, 1946, p. 615.

*Westergren, A.*: Nord. Lærebog i Intern Med. II. E. Munksgaard, Copenhagen, 1952, p. 134.

Uppsala 1958
Appelbergs Boktryckeri AB